International Journal of Clinical Trials
Nabi T et al. Int J Clin Trials. 2019 Aug;6(3):106-111
http://www.ijclinicaltrials.com
pISSN 2349-3240 | eISSN 2349-3259
DOI: http://dx.doi.org/10.18203/2349-3259.ijct20193213

Original Research Article

N-acetylcysteine treatment in viral-induced acute liver failure

Tauseef Nabi[1], Nadeema Rafiq[2]*

[1]Department of Endocrinology, Government Medical College, Srinagar, Jammu and Kashmir, India
[2]Department of Physiology, Government Medical College, Baramulla, Jammu and Kashmir, India

Received: 28 February 2019
Revised: 23 April 2019
Accepted: 04 May 2019

***Correspondence:**
Dr. Nadeema Rafiq,
E-mail: dr.nadeema@gmail.com

ABSTRACT

Background: Acute liver failure (ALF) is characterized by acute derangement of liver function and carries high mortality. Viral hepatitis is still one of the main causes of ALF in the India as well in world. A prospective case control study was carried with the aim to determine the effect of N-acetylcysteine (NAC) on survival of viral-ALF patients.
Methods: 37 patients with a diagnosis of viral-ALF were included in the study. 18 patients received NAC infusion for 72 hrs whereas 19 patients in control group received placebo. The variables evaluated were demographic, biochemical, outcome and length of hospital stay.
Results: Out of 37 viral-ALF patients, acute HEV-induced ALF (48.6%) was most common followed by HBV (24.3%) and HAV (21.6%). The two groups were comparable for the various baseline characteristics (age, INR, bilirubin, ALT, creatinine, albumin, grade of encephalopathy, mean grade of coma etc.). Use of NAC was associated with a shorter length of hospital stay of survived patients (p=0.024). A total of 20 of 37 (54.1%) patients died with ALF complications; 7 (38.9%) patients belonged to NAC group and 13 (68.4%) patients to control group (p=0.079). HEV induced ALF showed significant improved in survival than Non HEV induced ALF with NAC administration (p=0.022).
Conclusions: HEV was the most frequently cause of viral-ALF. Overall survival was not improved by NAC. HEV induced ALF showed significant improved in survival than Non HEV induced ALF with NAC administration. NAC reduced duration of hospital stay.

Keywords: Acute liver failure, Viral-ALF, Hepatic encephalopathy, Hepatitis E virus, N-acetylcysteine

INTRODUCTION

Acute liver failure (ALF) is a syndrome characterized by the development of hepatic encephalopathy (HE) together with signs of liver dysfunction, especially jaundice and coagulation disorders, in patients without previous liver disease.[1] Fortunately, it is a rare disease with 2000 to 3000 reported cases in the United States per year.[2] Reports from the developed world suggest an overall incidence of 1-8 cases per million people every year, yet it accounts for up to 7% of all liver-related deaths and is responsible for 6% of liver transplants.[2-4] However, spontaneous recovery is observed in up to 45% of ALF patients, and specific treatments for known etiologies can be effective.[5] The term acute liver failure is used to describe the development of coagulopathy, usually with an international normalized ratio (INR) of greater than 1.5, and any degree of HE in a patient without pre-existing cirrhosis and with an illness of less than 26 weeks duration.[6]

Etiology of ALF is heterogenous and shows wide geographical variation. The main etiological factor includes: viral, drugs including herbal and traditional

medications, autoimmune, toxin and indeterminate.[7] Acetaminophen overdose is the most common cause of ALF in the United States and Europe, whereas viral hepatitis is more common in Asia and Africa, but numerous other causes have been reported, including drug-induced liver injury, viral hepatitis, ischemic liver injury, Wilson's disease, and acute presentation of autoimmune hepatitis.[8,9]

Viral hepatitis which mostly include hepatotropic (HBV, HAV, HEV, HCV, HDV, HGV) and non-hepatotropic viruses (CMV, HSV, EBV etc.). Viral hepatitis is the commonest cause of ALF world-wide and in the Indian subcontinent alone it accounts for 90% of cases.[10] All primary hepatotropic viruses can cause ALF with a different incidence in different countries.[11,12] In developing world Hepatitis B (HBV) predominates as a cause, but in India, Pakistan, China and Southeast Asia, Hepatitis E (HEV) is now the most common cause of ALF.[13] HEV has a high predilection for pregnant women and development of ALF in pregnant women may further influence prognostic factors and decision to consider liver transplantation.[14] Acute hepatitis C seems to be a cause of ALF in Asia but not in Western countries.[15,16] More rare viral causes of ALF include, delta virus, cytomegalovirus (CMV), herpes simplex virus (HSV), and Epstein-Barr virus (EBV) infections.[17-21]

Mortality related to ALF can be attributed to three complications in particular: cerebral edema, multiorgan dysfunction syndrome, and sepsis. Liver has the unique ability to regenerate after acute, self-limiting injury. The overall management strategy starts with the identification of cause and an initial assessment of prognosis. Although many people recover with supportive treatment; orthotropic liver transplantation (OLT) remains the only definitive therapy for patients who are unable to achieve sufficient hepatocyte regeneration on supportive treatment. OLT has made a significant impact on survival of patients with ALF.[22,23] Therefore better cost effective alternatives are needed in locations where facility is not available. N-acetylcysteine (NAC) has a well-established role in paracetamol-induced ALF although it is now also recommended in selected cases of non-paracetamol ALF because of its multiple mechanisms of action. [24-27]

NAC is a thiol-containing agent that scavenges free oxygen radicals and replenishes cellular mitochondrial and cytosolic glutathione.[28,29] Its anti-inflammatory, antioxidant, inotropic, and vasodilating effect has been proved from various trials.[30,31] NAC may benefit patients either by improving systemic hemodynamics and tissue oxygen delivery or via other mechanisms.[32,33] Role of NAC in viral-ALF has not been studied in controlled trials. In this prospective study, we aimed to determine the role of NAC on survival in viral-ALF and also to evaluate the safety and efficacy of NAC and its impact on the duration of hospital stay at tertiary care centre in Kashmir (North India).

METHODS

It was a single centre prospective study of adult patients with viral-ALF. This study was carried out in the Department of Gastroenterology of Sher-i-Kashmir Institute of Medical Science (SKIMS), Soura, Jammu and Kashmir. The study was approved by the institutional ethical committee (SKIMS). Informed consent was obtained from all the recruited subjects.

Study subjects

Total of 37 consecutive patients with diagnoses of viral-ALF who fulfilled eligibility criteria were recruited in the study. This study was conducted over a period of three years from April 2011 to May 2014. Information regarding various demographics characteristics was taken through well structured questionnaires from all subjects. Besides a detailed history, physical examination and biochemical workup which included baseline investigations, liver function test (LFT), coagulogram of subjects were carried out.

Eligibility criteria

Inclusion criteria include patients having age >18years and ALF was defined as biochemical evidence of acute liver injury with INR ≥1.5 and any degree of encephalopathy caused by the illness of duration <26 weeks in a patient with no prior known liver disease and with established viral etiology.

Exclusion criteria include i) Drug-induced ALF, ii) Autoimmune ALF, iii) Acute on chronic liver failure, iv) ALF during pregnancy, iv) Hepatic shock.

Detailed study design

After ALF was diagnosed, a detailed history was taken for any hepatotoxic drug intake, including homeopathic, herbal medications and intravenous drug abuse. Blood samples of all the patients were taken for the etiological diagnoses, which included hepatitis B surface antigen (HBsAg), hepatitis B core IgM (HBc-IgM), hepatitis A virus IgM (HAV-IgM), and hepatitis E virus IgM (HEV-IgM), hepatitis D virus (IgG and IgM anti-HDV), anti HCV (hepatitis C virus), ANA (anti nuclear antibody), ASMA (anti smooth muscle antibody), Wilson profile (serum ceruloplasmin, serum copper) and iron profile. HSV (herpes simplex virus), CMV (cytomegalovirus) and EBV (Epstein barr virus) serology were done if non hepatotropic viruses were suspected as a cause of ALF. Imaging was obtained to rule out biliary processes, hepatic vascular abnormalities, and intrahepatic lesions. All the ethical considerations were taken care of during the study. Subjects were then randomized by simple random method into two groups.

NAC group

18 viral-ALF patients who fulfilled the eligibility criteria were treated with intravenous NAC for duration of 72 hours.

Control group

19 viral-ALF patients received 5% dextrose (placebo) infusion for 72 hours.

Study medication

After informed written consent was obtained from next of kin, the patients in NAC group were administered intravenous NAC with initial loading dose of 150 mg/kg over 1 hour, followed by 12.5 mg/kg/hr for 4 hours and then continuous infusion of 6.25 mg/kg/hr for remaining 67 hours. Patients in Control group were given 5% dextrose infusion (placebo) for 72 hours. All the ethical considerations were taken care of during the study. Patients were given the option of liver transplant (to be done at the hospital with transplantation facility) at various stages of study when indicated. No patient underwent OLT.

Supportive treatment

All patients were managed with the standard supportive care treatment.[34] The patients received treatment of and prevention for the complications of ALF. The treatment mainly involved continuous intravenous dextrose to prevent hypoglycemia; proton pump inhibitors for stress-related ulcers and lactulose enema. With the development of advanced HE, intensive care management, fluid and electrolyte balance, midazolam sedation and mannitol infusion in case of raised intracranial pressure. Intracranial hypertension was diagnosed clinically in the presence of clinical signs such as abnormal pupillary reflexes, hypertonia or decerebrate posturing. Fresh frozen plasma and vitamin K was given in only those patients who had a spontaneous bleed. Blood and urine cultures were obtained in suspected cases of sepsis, which were then treated as per sensitivity. Renal impairment was defined as serum creatinine level of more than 1.5 mg/dl. Response to treatment was monitored clinically (grade of encephalopathy) and biochemically (bilirubin, PT, INR etc.). In addition, morbidity and mortality was also assessed. Patients were followed till discharge or death in hospital.

Statistical analyses

Frequency distribution was assessed in terms of means±SD for quantitative variables and number (percentages) for categorical variables. In univariate analysis, the categorical variables were compared by using χ^2 test or Fisher exact test where appropriate. For continuous variables, the independent sample t-test was used. P values <0.05 was considered statistically significant. All the analyses were performed by the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA, version 21.0).

RESULTS

There were 37 patients of viral-ALF in total. Table 1 demonstrates the etiologies of viral-ALF. Acute HEV-induced ALF (48.6%) was most common followed by hepatitis B (24.3%) and A (21.6%). One patient each of CMV (cytomegalovirus) and HSV (herpes simplex virus). No patient had HDV and HCV related ALF.

Table 1: Etiology of viral induced acute liver failure (n=37).

Etiology	Total
	N (%)
Acute hepatitis E	18 (48.6)
Acute hepatitis A	8 (21.6)
Acute hepatitis B	9 (24.3)
CMV	1 (2.7)
EBV	1 (2.7)

There were 18 patients in the NAC group and 19 patients in control group. Table 2 shows the distribution of baseline characteristics (both categorical and continuous) of two groups of viral-ALF. The mean age in NAC group was 35.5±16.2 years and in control group was 37.9±20.2 years (p=0.639). Majority of the patients were males (59.5%) and they were equally distributed between two groups. Coma grade at the time of admission showed that majority of patients (56.8%) had grade I and II encephalopathy. The patients in both the groups were comparable for the different grade of encephalopathy (p=0.276). The two treatment groups did not differ significantly with respect to fever, vomiting, creatinine, MELD score, interval between jaundice and encephalopathy, mean grade of coma and biochemical measures of liver injury (INR, bilirubin, AST, ALT, and albumin).

The mean number of days of admission in hospital of survived patients in NAC group was 8.4±4.2 versus 11.9±4.8 in Controls. The difference was statistically significant (p=0.024) (Table 3). A total of 20 of 37 (54.1%) patients died with ALF complications; 7 (38.9%) patients belonged to NAC group and 13 (68.4%) patients to Control group (Chi sq=3.151; p=0.079).

More patients (61%) survived in NAC group than in the Control group (31.6%) and the difference was not statistically significant (Table 4). When survival was considered between different etiologies of viral-ALF, HEV induced ALF showed significant improved in survival than Non HEV induced ALF with NAC administration (p=0.022) (Table 5).

Logistic regression analysis was performed in order to study the role of independent risk factors on mortality in viral-ALF patients. In the study age >50 years, III – IV grade of encephalopathy, renal impairment, MELD score >31 and Non HEV induced ALF were the independent prognostic factors determining mortality.

Table 2: Baseline characteristics of study subjects in the two groups of viral-ALF.

Characteristics	NAC group (n=18)	Control group (n=19)	P value*
Categorical variables [N (%)]			
Female gender	7 (38.9)	8 (42.1)	0.845
Hepatic-encephalopathy			
Grade I	7 (38.9)	5 (26.3)	0.276
Grade II	6 (33.3)	3 (15.8)	
Grade III	2 (11.1)	5 (26.3)	
Grade IV	3 (16.7)	2 (10.5)	
Fever	5 (27.8)	8 (42.1)	0.369
Vomiting	4 (22.2)	5 (26.3)	0.763
Continuous variables [mean±SD]			
Age (years)	35.5±16.2	37.9±20.2	0.693
INR	2.2±0.7	2.0±0.9	0.457
Bilirubin (mg/dl)	18.1±8.9	20.8±9.5	0.379
AST (mg/dl)	1014±784	967±512	0.829
ALT (mg/dl)	1110±678	945±589	0.435
Albumin (g/dl)	2.7±0.6	2.9±0.5	0.277
Creatinine (mg/dl)	1.3±0.5	1.37±0.6	0.703
Interval between jaundice and encephalopathy (days)	32±15.8	35±16.2	0.572
Grade of coma	2.4±0.9	2.2±1.1	0.550
MELD score	28.9±7.9	27.4±5.6	0.507

*P value <0.05 is considered statistically significant; n=number; SD=standard deviation.

Table 3: Length of hospital stay in NAC group and controls.

	NAC group Mean±SD (range)	Control group Mean±SD (range)	P value*
Duration of hospital stay of survived patients (days)	8.4±4.2 (6-14)	11.9±4.8 (8-17)	0.024

*P value <0.05 is considered statistically significant.

Table 4: Survival of study subjects in viral-ALF.

	NAC group	Control group	P value*
	N (%)	N (%)	
Survival	11 (61.1)	6 (31.6)	0.079

*P value <0.05 is considered statistically significant.

Table 5: Survival for study subjects stratified by etiology of viral-ALF.

Etiology	NAC group	Control	P value*
HEV n=18	1, 90% N=10	5, 37.5 % N=8	0.022
Non HEV n=19	6, 25% N=8	8, 27.3% N=11	0.912

*P value <0.05 is considered statistically significant.

DISCUSSION

ALF is rare syndrome, characterised by an acute abnormality of liver function tests in an individual without underlying chronic liver disease. The disease process is associated with development of a coagulopathy of liver etiology and altered mentation i.e., HE.[35] Trying to determine etiology is essential, however, as outcomes and the use of antidotes depend on the identification of the causative process. OLT has now become an established treatment option in patients with ALF. Due to lack of OLT facility NAC has emerged as a beneficial treatment for non-paracetamol ALF.[25-27] Role of NAC in viral-ALF has not been studied in controlled trials. So the prospective study was carried out to determine the role of NAC on mortality in viral-ALF and also to evaluate the safety and efficacy of NAC and its impact on the duration of hospital stay at tertiary care centre in Kashmir (North India).

In our study HEV was etiologically associated with ALF in 48.6% patients, HBV in 24.3%. HEV is endemic in Kashmir and is the most common cause of acute viral hepatitis in this and other endemic regions of the world.[10,13,36,37] Similarly, the proportion of HBV related

ALF cases has not changed over the years, comprising 24.3% of cases in the previous series.[13] HAV constituted 21.6% of ALF cases in the present study. Das et al reported higher percentage of HAV (29.8%) as cause for ALF.[38]

In this prospective case control trial, more patients (61%) survived in NAC group than in the control group (31.6%) but we found no significant improvement in the survival of patients who were treated with NAC (p=0.079). When survival was considered between different etiologies of viral-ALF, HEV induced ALF showed significant improved in survival than Non HEV induced ALF with NAC administration (p=0.022). Furthermore, the use of NAC was safe and was associated with a shorter length of hospital stay in survived patients (p=0.024).

The previous study by us showed that NAC improved the overall survival in non-acetaminophen induced ALF with more favourable effect on drug induced ALF.[25] Other studies also reported NAC improved transplant-free survival in early stage non-acetaminophen ALF in adults and childrens.[26,27,39-41] The favourable effect of NAC on HEV induced ALF could because HEV related ALF has better outcome than Non HEV as shown in other study.[13]

To the best of our knowledge, role of NAC in viral-ALF has not been studied in prospective controlled trials. The major strengths of this study include prospective cases and controls. Some of the limitations of our study include small sample size, single centre study and the duration of follow up was short (hospital stay till discharge or death in the hospital).

ACKNOWLEDGEMENTS

We thank the Department of Gastroenterology of Sher-i-Kashmir Institute of Medical Science.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Trey C, Davidson CS. The management of fulminant hepatic failure. Prog Liver Dis. 1970;3:282-98.
2. Hoofnagle JH, Carithers RL Jr, Shapiro C, Ascher N. Fulminant hepatic failure: summary of a workshop. Hepatology. 1995;21(1):240–52.
3. Bower WA, Johns M, Margolis HS, Williams IT, Bell BP. Population-based surveillance for acute liver failure. Am J Gastroenterol. 2007;102:2459-63.
4. Rockville. Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation; 2007.
5. Lee WM, Squires Jr RH, Nyberg SL, Doo E, Hoofnagle JH. Acute liver failure: summary of a workshop. Hepatology. 2008;47(4):1401-15.
6. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013;369:2525–34.
7. Ostapowicz G, Fontana R J, Schiodt F V. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002;137:947–54.
8. Lee WM. Etiologies of acute liver failure. Semin Liver Dis. 2008;28(2):142-52.
9. Sugawara K, Nakayama N, Mochida S. Acute liver failure in Japan: definition, classification, and prediction of the outcome. J Gastroenterol. 2012;47(8):849-61.
10. Acharya SK, Dasarathy S, Kumer TL, Sushma S, Prasanna KS, Tandon A et al. Fulminant hepatitis in tropical population: clinical course, cause, and early predictors of outcome. Hepatology. 1996;23:1448-55.
11. Tibbs C, Williams R. Viral causes and management of acute liver failure. J Hepatol. 1995;22(Suppl.1):68-73.
12. Fagan EA, Williams R. Fulminant viral hepatitis. Br Med Bull. 1990; 46: 462-80.
13. Khuroo MS, Kamili S. Aetiology and prognostic factors in acute liver failure in India. J Viral Hepat. 2003; 10: 224–31.
14. Khuroo MS, Teli MR, Skidmore S, Sofi MA, Khuroo MI. Incidence and severity of viral hepatitis in pregnancy. Am J Med. 1981;70:252–5.
15. Yoshiba M, Dehara K, Inoue K, Okamoto H, Mayumi M. Contribution of hepatitis C virus to non-A, non-B fulminant hepatitis in Japan. Hepatology. 1994;19:829–35.
16. Farci P, Alter HJ, Shimoda A, Govindarajan S, Cheung LC, Melpolder JC, et al. Hepatitis C virus-associated fulminant hepatic failure. N Engl J Med. 1996;335:631–4.
17. Govindarajan S, Chin KP, Redeker AG, Peters RL. Fulminant B viral hepatitis: Role of delta agent. Gastroenterology. 1984;86:1417–20.
18. Peters DJ, Greene WH, Ruggiero F, McGarrity TJ. Herpes simplex-induced fulminant hepatitis in adults. Dig Dis Sci. 2000;45(12):2399-404.
19. Farr RW, Short S, Weissman D. Fulminant hepatitis during herpes simplex virus infection in apparently immunocompetent adults: Report of two cases and review of the literature. Clin Infect Dis. 1997;24:1191–4.
20. Mellinger JL, Rossaro L, Naugler WE, Nadig SN, Appelman H, Lee WM, et al. Epstein–Barr virus (EBV) related acute liver failure: a case series from the US Acute Liver Failure Study Group. Dig Dis Sci. 2014;59(7):1630-7.
21. Srivastava P. Acute Liver Failure: due to Epstein Barr Virus infection-A Case Report. J Hep. 2015;2:1.
22. Lee WM. Acute liver failure in the United States. Semin Liver Dis. 2003;23:217–26.

23. Schiodt FV, Atillasoy E, Shakil AO, Schiff ER, Caldwell C, Kowdley KV. Etiology and outcome for 295 patients with acute liver failure in the United States. Liver Transpl Surg. 1999;5(1):29-34.
24. Polson J, Lee WM. American Association for the Study of Liver Disease. AASLD position paper: the management of acute liver failure. Hepatology. 2005;41:1179–97.
25. Nabi T, Nabi S, Rafiq N, Shah A. Role of N-acetylcysteine treatment in non-acetaminophen-induced acute liver failure: A prospective study. Saudi J Gastroenterol. 2017;23(3):169–75.
26. Lee WM, Hynan LS, Rossaro L Fontana RJ, Stravitz RT, Larson AM, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. Gastroenterology. 2009;137:856–64.
27. Darweesh SK, Ibrahim MF, El-Tahawy MA. Effect of N-acetylcysteine on mortality and liver transplantation rate in non-acetaminophen-induced acute liver failure: a multicenter study. Clin Drug Investig. 2017;37(5):473-82.
28. Cotgreave IA. N-acetylcysteine pharmacological considerations and experimental and clinical applications. Adv Pharmacol. 1997;38:205-27.
29. Kharazmi A, Nielsen H, Schiotz PO. N-acetylcysteine inhibits human neutrophil and monocyte chemotaxis and oxidative metabolism. Int J Immunopharmacol. 1988;10:39-46.
30. Harrison P, Wendon J, Williams R. Evidence of increased guanylate cyclase activation by acetylcysteine in fulminant hepatic failure. Hepatology. 1996;23(5):1067–72.
31. Harrison PM, Wendon JA, Gimson AE, Alexander GJ, Williams R. Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. N Engl J Med. 1991;324(26):1852–7.
32. Rank N, Michel C, Haertel C. N-acetylcysteine increases liver blood flow and improves liver function in septic shock patients: results of a prospective, randomized, double-blind study. Crit Care Med. 2000;28:3799–807.
33. Bémeur C, Vaquero J, Desjardins P, Butterworth RF. N-acetylcysteine attenuates cerebral complications of non-acetaminophen-induced acute liver failure in mice: antioxidant and anti-inflammatory mechanisms. Metab Brain Dis. 2010;25(2):241-9.
34. Lee WM, Larson AM, Stravitz RT. AASLD Position Paper: The Management of Acute Liver Failure: Update 2011. http://www.aasld.org/practiceguidelines/Documents/AcuteLiverFailureUpdate2011.pdf. Accessed Jan 2019.
35. European Association for the Study of the Liver. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol. 2017;66(5):1047-81.
36. Khuroo MS, Duermeyer W, Zargar SA, Ahanger MA, Shah MA. Acute sporadic hepatitis in India. Am J Epidemiology. 1983:118:360–4.
37. Ramalingaswami V, Purcell RH. Waterborne Non-A, non-B hepatitis. Lancet. 1988;1:571–3.
38. Das AK, Begum T, Kar P, Dutta A. Profile of Acute liver failure from North-east India and its differences from other parts of country. Eurosian Journal of Hepato-Gastroenterology. 2016;6(2):111–5.
39. Ben-Ari Z, Vaknin H, Tur-Kaspa R. N-acetylcysteine in acute hepatic failure (non-paracetamol-induced). Hepatogastroenterology. 2000;47(33):786–9.
40. Sklar GE, Subramaniam M. Acetylcysteine treatment for non–acetaminophen-induced acute liver failure. Annals of Pharmacotherapy. 2004;38(3):498-501.
41. Mumtaz K, Azam Z, Hamid S, Abid S, Memon S, Shah HA, et al. Role of N‐Acetylcysteine in adults with non‐acetaminophen‐induced acute liver failure in a center without the facility of liver transplantation. Hepatol Int. 2009;3:563‐70.

Cite this article as: Nabi T, Rafiq N. N-acetylcysteine treatment in viral-induced acute liver failure. Int J Clin Trials 2019;6(3):106-11.